REMARKS

Claims 1, 5-13, 19-27, and 42-45 are pending in the subject application. By this Amendment, applicants have amended claims 1, 42 and 44, and canceled claims 20 and 27 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in this or another application.

The amendments to claims 1, 42 and 44 are supported in the specification at, *inter alia*, page 2, line 18 to page 3, line 29; page 4, lines 30-35; page 5, line 6 to page 6, line 10; page 13, line 25 to page 15, line 5; page 16, line 17 to page 18, line 11; page 26, lines 13-20; and Figure 1. Thus, applicants maintain that these amendments do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 1, 5-13, 19, 21-26, and 42-45, as amended, will be pending and under examination.

The Invention

The invention claimed in the subject application is directed to compositions comprising an admixture of two peptidyl compounds, wherein one compound retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell, and the other compound retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate. The relative mass ratio of the compounds in the admixture ranges from about 100:1 to about 1:100, and the composition is effective to inhibit HIV-1 infection of the CD4+ cell. The invention also provides methods of inhibiting HIV-1 infection of a CD4+ cell comprising contacting the CD4+ cell with amounts of the instant compositions, or alternatively, contacting the CD4+ cell with a first peptidyl compound and a second peptidyl compound, effective to inhibit HIV-1 infection of the CD4+ cell.

Double Patenting Rejections

The Examiner rejected claims 1, 5-13, 19, 21-26 and 42-45 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of U.S. Patent No. 6,692,745 B2 for reasons of record.

In response, applicants respectfully traverse this obviousness-type double patenting rejection. Nevertheless, without conceding the correctness of the Examiner's position, applicants will consider filing a terminal disclaimer if the claims under examination are otherwise allowable.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 1, 5-13, 19, 20-27 and 42-45

The Examiner rejected claims 1, 5-13, 19, 21-26 and 42-45 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a composition comprising an admixture of two peptidyl compounds, and a method comprising use of this composition, allegedly does not reasonably provide enablement for an admixture of two non-peptidyl compounds. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Examiner also rejected claims 20 and 27 under 35 U.S.C. §112, first paragraph, because the specification is allegedly not enabling for a composition comprising an admixture of two non-peptidyl compounds, and a method comprising use of the composition.

The Examiner stated that applicants' arguments have been carefully considered but fail to persuade. The Examiner also stated that applicants' substantive arguments are primarily directed to the following two points regarding the enablement of a composition, and method of using the composition, comprising non-peptidyl agents that inhibit HIV infection of cells:

(a) The specification provides a rational screening strategy based on the resonance energy transfer (RET) assay for identifying compounds that inhibit fusion of HIV-1. For example, Litwin et al. (PCT International Publication No. WO 02/079186) use the RET assay to identify non-peptidyl compounds that inhibit HIV-1 infection by binding the CCR5 receptor of the virus and thereby blocking the interaction between gp120 and CD4. Once non-peptidyl agents are identified by routine screening (e.g., using the RET assay), another routine assay could be performed in order to determine the mechanism underlying the non-peptidyl agents' activity, for example, the binding of the non-peptidyl agent to an epitope of CD4 or gp41. Since these screening processes are routine, they not constitute undue experimentation.

(b) The citation of Gait and Karn (1995) is without merit because the state of the art in HIV therapeutics, as of the date of applicants' invention (January 28, 2000), had changed from what it was in 1995. Further, the teachings of Gait and Karn relate to reverse transcriptase inhibitors and protease inhibitors, whereas the claims of the subject application relate to compounds that inhibit binding of HIV-1 envelope glycoproteins to cell surface receptors.

In response to point (a), the Examiner conceded that one could identify, without undue experimentation, non-peptidyl agents that generally inhibit binding of gp120 to a CD4 receptor. The Examiner asserted that it would, however, require undue experimentation for one to have to: (1) identify a non-peptidyl agent that inhibits HIV infection, and (2) determine the agent's mechanism of action. The Examiner noted that the claims require the use of a non-peptidyl agent that binds an epitope of gp41. The Examiner also asserted that one of skill would not expect applicants' "routine" experimentation to end with step (2) on a first try. The Examiner further stated that one would expect to continue testing agents to determine their mechanism of action, specifically their ability to bind a gp41 epitope (as claimed in claim 1). The Examiner concluded that due to the numerous mechanisms that can be used to inhibit HIV binding and infection, it would require undue experimentation to find a non-peptidyl agent that binds a gp41 epitope to use in applicants' method. The Examiner further noted that the specification does not provide guidance on how to streamline this process of discovery such that it would be routine experimentation.

The Examiner also conceded, in response to point (b) above, that the teachings of Gait and Karn (1995) regarding the unpredictability of inhibiting HIV infection using non-peptidyl agents are not directly pertinent to the instant claims in view of (i) the state of the art at the time of the invention, and (ii) Gait and Karn's use of non-peptidyl agents that target other aspects of HIV infection.

In response, applicants respectfully traverse the above "enablement" rejections. Nevertheless, without conceding the correctness of the Examiner's position, applicants note that independent claims 1, 42 and 44, as amended herein, are directed to compositions comprising an admixture of two peptidyl compounds, and methods of inhibiting HIV-1 infection of a CD4+ cell comprising contacting the CD4+ cell with amounts of the instant compositions, or alternatively, contacting the CD4+ cell with a first peptidyl compound and a second peptidyl compound, effective to inhibit HIV-1 infection of the CD4+ cell.

As noted above, claims 1, 42 and 44, as amended herein, are fully supported by the specification as filed. Moreover, the Examiner has acknowledged on page 2 of the Final office Action that the specification is enabling for a composition comprising an admixture of two peptidyl compounds, and a method comprising use of this composition. Thus, independent claims 1, 42 and 44, as amended herein, are directed to subject matter which the Examiner has stated is enabled by the specification. Applicants maintain, therefore, that this ground of rejection should be withdrawn.

Applicants note that claims 5-13, 19, 21-26, 43 and 45 depend, directly or indirectly, from claims 1, 42 or 44, and therefore necessarily possess all the elements of claims 1, 42 or 44. Applicants respectfully submit, therefore, that the remarks made above regarding independent claims 1, 42 and 44 also obviate the rejection of claims 5-13, 19, 21-26, 43 and 45 on the ground of lack of enablement.

Further, applicants note that claims 20 and 27 have been canceled herein without disclaimer or prejudice, thereby rendering the rejection of these claims moot.

Accordingly, based on the foregoing remarks, applicants respectfully request that the Examiner reconsider and withdraw this "enablement" ground of rejection.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 1, 5-13, 19, 21-26 and 42-45 under 35 U.S.C. §103(a) as allegedly unpatentable over Allaway et al.

(U.S. Patent No. 5,817,767; herein, "Allaway") in view of Bolognesi et al. (U.S. Patent No. 5,464,933; herein, "Bolognesi"). The Examiner stated that applicants' arguments in response to this rejection, which was previously made with regard to claims 24-26, have been carefully considered but fail to persuade.

The Examiner noted applicants' argument that Allaway fails to disclose all of the claimed elements of the invention, namely, an agent that binds an epitope of the gp41 fusion intermediate. The Examiner also noted applicants' reference to Allaway's disclosure of the use of monoclonal antibody 2F5 which binds gp41 prior to fusion. The Examiner further stated that in view of applicants' argument, the anticipation rejection was withdrawn but that the claims still remain obvious over the combination of Allaway and Bolognesi.

The Examiner also noted applicants' argument that because Allaway does not teach the use of an agent that binds an epitope of a gp41 fusion intermediate, but rather teaches binding to epitopes of gp41 generally, there is no motivation to use the peptides of Bolognesi which bind to epitopes of gp41 fusion intermediates. In response to this argument, the Examiner additionally stated that whereas the Office recognizes that Allaway does not specifically mention the use of agents that bind epitopes of gp41 fusion intermediates, Allaway does teach the use of agents that bind gp41 generally. The Examiner stated that, furthermore, Allaway's teachings are not limited to the disclosure of monoclonal antibody 2F5 as the only example. The Examiner asserted that one of ordinary skill in the art would have been motivated to use the peptides of Bolognesi in Allaway's method because Allaway teaches the use of agents that bind gp41. The Examiner noted that whether gp41 is in its original state or in a fusion intermediate state, it remains gp41. The Examiner also contended that although Allaway does not explicitly distinguish between the two conformations, one would have known that gp41 occurs in two conformations.

The Examiner asserted that one would have had a reasonable expectation of success that the use of Bolognesi's peptides in lieu of Allaway's agent would have interfered with gp41 fusion because both agents bind gp41, whether in the original state or in the fusion intermediate state.

The Examiner also stated that regarding the Fab fragment, Allaway is silent on the Fab portion of the antibody as a compound that interferes with gp120 binding to CD4. The Examiner further stated that it is, however, well known in the art that the Fab fragment is the portion which binds epitopes because it contains the variable regions. The Examiner asserted that one of ordinary skill in the art would have been motivated to use the portion of the antibody that binds epitopes and would have had a reasonable expectation of success given the nature of the Fab fragment. The Examiner concluded that the invention is therefore obvious over Allaway in view of Bolognesi.

In response, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants note that, according to M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic requirements must be satisfied. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference, or references when combined, must teach or suggest all the claim limitations.

For the reasons set forth below, applicants maintain that the

Examiner has failed to satisfy at least the second prong of the requirements for establishing a *prima facie* case of obviousness.

In this regard, applicants note that, as disclosed in the specification, the combination of (1) a peptidyl compound (exemplified by CD4-IgG2) which retards attachment of HIV-1 to a CD4+ cell by retarding binding of HIV-1 gp120 envelope glycoprotein to CD4 on the surface of the CD4+ cell, and (2) a peptide (exemplified by T-20) which retards gp41 from adopting a conformation capable of mediating fusion of HIV-1 to a CD4+ cell by binding noncovalently to an epitope on a gp41 fusion intermediate, synergistically inhibits fusion of HIV-1 to CD4+ cells (see Figures 1-3). That is, the combined effect of these two peptidyl compounds when administered concurrently is greater than their additive effects. Thus, analysis of dose-response curves for the compounds used individually and in combination, as measured by the RET membrane fusion assay, revealed that the combinations was potently synergistic in inhibiting Env-mediated membrane fusion of HIV-1 to CD4+ cells (see the specification at page 26, lines 13-20, and Figure 1).

The degree of synergy was quantified using the Combination Index (CI) method, wherein a CI value greater than 1 indicates antagonism, a CI equal to 1 indicates a purely additive effect, and CI less than 1 indicates a synergistic effect (see the specification at page 26, lines 8-10). This quantification confirmed potent synergies over broad ranges of inhibitor ratios and concentrations, with CI values as low as 0.20 under optimal conditions (see the specification at page 26, line 22 to page 27, line 3, and Figure 2). The observed synergies translated into 17- and 5-fold reductions in the amounts of CD4-IgG2 and T-20, respectively, needed to achieve 95% inhibition of viral entry, and even greater dose reductions were observed at higher levels of inhibition (see the specification at page 27, lines 14-24, and Figure 3).

Applicants note that the observed synergy between the two classes of entry inhibitors was surprising and unexpected. Indeed, the specification describes the degree of synergy as "remarkable," and notes that CI values of 0.2 are rarely observed for combinations involving anti-HIV-1 antibodies, reverse transcriptase inhibitors, or protease inhibitors (see page 26, line 32 to page 27, line 3).

Applicants maintain that the combination of Allaway and Bolognesi does not provide any reasonable expectation of success that a composition comprising (1) a peptidyl compound that retards binding of gp120 to CD4 on the surface of the CD4+ cell, and (2) a peptidyl compound that binds to an epitope on a gp41 fusion intermediate, would exhibit synergistic inhibition of HIV-1 infection, compared to the individual inhibitory effects of these two compounds.

Similarly, the combination of Allaway and Bolognesi provides no reasonable expectation of success that synergistic inhibition of HIV-1 infection would be observed in a method comprising the use of the instant two peptidyl classes of HIV-1 entry inhibitors.

Since the combination of Allaway and Bolognesi provides no reasonable expectation that the claimed invention would succeed, applicants maintain that the second requirement for establishing a *prima facie* case of obviousness has not been satisfied. Thus, applicants maintain that the unexpected synergistic effect exhibited by the composition comprising the instant peptidyl compounds renders the claimed invention nonobvious over Allaway and Bolognesi. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Conclusion

In view of the remarks and arguments made hereinabove, applicants respectfully submit that the grounds of rejection set forth in the February 9, 2005 Final Office Action have been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw these grounds of rejection, and earnestly solicit allowance of all claims pending in the subject application, namely claims 1, 5-13, 19, 21-26, and 42-45, as amended.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed fee of FIVE HUNDRED AND TEN DOLLARS (510.00) for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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